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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/398,897	09/20/1999	RENJI YANG	0109015/016	1629

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SMR

Office Action Summary	Application No.	Applicant(s)	
	09/398,897	YANG ET AL.	
	Examin r	Art Unit	
	Robert C. Hayes, Ph.D.	1647	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,12,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,12,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. The amendment filed 07/14/03 has been entered.

2. The rejection of claims 1, 4-5, 12 & 15-16 under 35 U.S.C. 112, first paragraph, for new matter is withdrawn due to the amendment of the claims.

3. Applicant's arguments filed 07/14/03 have been fully considered but they are not deemed to be persuasive.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1, 4-5, 12 & 15-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nakafuka et al (IDS Ref #26), in view of Weiss et al. (U.S. Patent 5,851,832; IDS Ref #2), for the reasons made of record in Paper NOs: 11 (mailed 4/18/02) and 17 (mailed 11/19/02), and as follows.

Applicants argue on page 9-12 of the response that the claims have been amended to recite "an 'adhesion' culture of neural precursor cells", that "Nakafuku et al. teaches use of serum to initiate an *adhesion* culture of neuroepithelial precursor cells [emphasis added]", but then argues that the "serum-free culture of Weiss et al., however, uses a 'suspension' culture". However, it should be noted that the teaching of Weiss relied upon in the instant rejection

remains teaching the benefits of "serum-free" culture conditions, as already extensively made of record. In contrast, the teachings of Nakafuku et al teach an "adhesion" culture, as Applicants' correctly point out. Thus, Applicants' arguments are not on point, and therefore, moot.

It is noted that ways to possibly overcome this rejection were discussed during the 4/30/03 interview, in which merely amending the claims to "adhesion" cultures would not obviate this rejection. Thus, it appears Applicants have chosen to ignore the Examiner's suggestions.

In summary, Nakafuka et al teach a method of producing stable mammalian neural precursor cells *in vitro* using adhesion cultures comprising preparing cultures of E12 embryonic rat neuroepithelial/neural precursor cells in Dulbecco's modified Eagle's medium with serum that reasonably contains mitogens, such as α FGF, bFGF, EGF and/or TGFα, followed by transfection with the same *mycer* construct as used in the instant application (i.e., c-myc cDNA construct fused to the ligand binding domain of an estrogen receptor; pg. 155 & 156; as it relates to claims 1a-c & 12a-c); thereby, establishing the clonal cell line, MNS-57. These MNS-57 cells were further cultured in the presence of a second mitogen, bFGF or EGF, in DF medium containing β-estradiol/ β-E2 (i.e., pgs. 155 & 157-159; Figs. 3 & 4; as it relates to claims 1d & 12d). However, Nakafuka et al. do not teach initial culturing of these neural precursor cells in medium that is serum-free, nor a method producing human neural precursor cells.

Weiss et al. teach that "a preferred embodiment for proliferation of neural stem cells is to use a defined serum-free culture medium, as serum tends to induce differentiation and contains unknown components" (col. 16, lines 23-26; as it relates to claims 1a & 12a). "The culture

medium is supplemented with at least one proliferation-inducing growth factor" (col. 16, lines 41-42), in which "[p]referred proliferation-inducing growth factors include EGF and TGFα" (col. 16, lines 56-57; as it relates to claims 1b & 12b). Weiss also teach use of human pluripotent embryonic stem cells (cols. 13 & 15-16; as it relates to claims 4-5 & 15-16). However, Weiss et al. do not disclose transfection of neural precursor/stem cells with c-myc constructs fused to steroid/thyroid hormone receptor ligand binding domains to form stable cell lines.

It would have been obvious to one of ordinary skill in the art at the time of filing Applicants' invention to modify Nakafuka's method of producing mammalian neural precursor/stem cells by using serum-free medium and culturing neural precursor cells in the presence of the first mitogen, EGF or TGFα, as taught by Weiss, in order to prevent premature differentiation of these neural precursor cells (which include Weiss' human pluripotent embryonic stem cells; as it relates to claims 4-5 & 15-16) prior to being transfected with Nakafuka's c-myc construct fused with the ligand binding domain of an estrogen receptor, which results in immortalization of these cells. Nakafuka's step (d) can subsequently be carried out using the second mitogens, aFGF or bFGF, along with β-estrodiol/ β-E2, to more accurately determine the effects of these defined components on the differentiation potential to neuronal-restricted cells, or alternatively to glial-restricted cells, etc.

Claims 1, 4-5, 12 & 15-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nakafuka et al (IDS Ref #26), in view of Weiss et al. (U.S. Patent 5,851,832; IDS Ref #2) as applied to claims 1, 4-5, 12 & 15-16 above, and further in view of Eilers et al (IDS Ref #20)

and/or Evans et al (1988), for the reasons made of record in Paper NOs:11 (mailed 4/18/02) and 17 (mailed 11/19/02), and as discussed above.

In summary, Nakafuka et al. and Weiss et al. are as described above. However, neither Nakafuka et al. nor Weiss et al. teach use of Nakafuka's c-myc constructs fused to other steroid/thyroid hormone receptor ligand binding domains.

Eilers et al. teach that a "similar chimaera, *mycgr*, that contains the sequence that encodes the hormone [ligand] -binding domain of the rat glucocorticoid receptor fused to the 3' end of *myc* transforms these cells in a glucocorticoid-dependent manner (pg. 67, 1st *pp*; as it relates to claims 1 & 12).

Evans is a review describing the well known ligand binding domains of steroid/thyroid hormone receptors (e.g., pg. 891; as it relates to estrogen, androgen, progesterone, glucocorticoid, thyroid hormone, retinoid and ecdysone receptors and their respective ligands/myc-activating chemicals in claims 1c-d & 12c-d).

It would have been obvious to one of ordinary skill in the art to produce stable mammalian/human neural precursor cells using the method of Nakafuka et al. in view of Weiss et al. modified using any well known steroid/thyroid hormone receptor ligand binding domain fused to Eilers' c-myc constructs, because Eilers et al teach that "similar chimaeras" transform cells in a steroid/thyroid hormone-dependent manner.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RCH

Robert C. Hayes, Ph.D.
January 8, 2003

Gary d Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
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